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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,505	07/02/2002	Klaus Braun	4121-133	6804

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 11/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,505	BRAUN ET AL.	
	Examin r	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,17,18 and 20* is/are rejected.

7)☒ Claim(s) *12,14-16 and 19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 July 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0602* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Applicant's election with traverse of the sequence of SEQ ID NO:6 in the paper filed August 14, 2003 is acknowledged. The traversal is on the ground(s) that the sequences for which restriction was required have the same technical relationship and function, and therefore only one invention forming a single general inventive concept is involved. This is not found persuasive because lack of unity is present where a single claim defines alternatives where no common structure is present and where all the alternatives do not belong to a recognized class of chemical compounds. See MPEP 1850 under "D. Markush Practice". Further, lack of unity exists where the claims do not avoid the prior art. See MPEP 1850 under "A. Independent and Dependent Claims". Applicants also contend that it is not an undue burden of search "to run seven amino acid sequences through a BLAST program offered free on the web." However, this is not a complete search of a sequence as defined by Office practice, which involves an STN search, search in the U.S. patent application sequence databases (in the patented, published, and pending application files), and search in the Geneseq, Swissprot, PIR, and SPTREMBL sequence databases, as well as text searches in the U.S. patent, foreign patent, and commercial databases. Finally, group policy is to search one sequence per application.

The requirement is still deemed proper and is therefore made FINAL.

2. The Sequence Listing filed January 15, 2002 is objected to because it was not filed with a statement that the content of the paper copy and the computer readable copy are the same as required by 37 CFR 1.821(f). Correction is required.

The Sequence Listing filed January 15, 2002 was approved by STIC for matters of form.

3. The drawings are objected to because SEQ ID NOS need to be inserted after every sequence subject to the sequence disclosure rules. See 37 CFR 1.821(d). The SEQ ID NOS may

be inserted into the drawings themselves, or more preferably into the Brief Description of the Drawings at pages 9-10 of the specification. Extraneous information, such as the website address and the reference to "Page 1 of 1", needs to be removed from Figure 6. "Table 1" has been grouped with the Figures. The table either needs to be deleted from the figures and re-inserted as part of the specification, or it needs to be re-labeled as a figure (with the other figures being re-labeled accordingly) and the Brief Description of the Drawings needs to be amended in order to refer to the new drawing. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

4. The disclosure is objected to because of the following informalities: SEQ ID NOS need to be inserted after every sequence subject to the sequence disclosure rules. See 37 CFR 1.821(d). Appropriate correction is required.

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 17 and 18 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. A "Use" is not a statutory class of invention.

6. Claims 2, 3, 5, 7, 9-11, 13, 17, and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There is no antecedent basis in the claims for the phrase "the plasma membrane" at claim 2, line 2. While independent claim 1 refers to a cell membrane, it does not use the terminology "plasma membrane". The term "derivative" at claim 3, line 2, is indefinite because it is not clear what constitutes a "derivative" of penetratin. It is

not clear what degree of functional and/or structural similarity a compound must have with penetratin in order to constitute a "penetratin derivative" and therefore be encompassed within the scope of the claim. The term is not defined in the claim, the specification, or the art. The phrase "one of the penetratins" in claim 4 is unclear because there is no mention in any of the claims upon which claim 3 depends that plural penetratins can be present in the conjugate. It is not clear if claim 4 is requiring that plural penetratins be present in the conjugate. At claim 5, the word "and" should be inserted before the last line so that standard Markush terminology is used. At claim 7, line 2, "and/or" should be changed to "and" so that standard Markush terminology is used. At claim 9, the phrase "if applicable" is indefinite because the claim does not set forth any standards with which to determine whether or not a spacer should be present. It is suggested that the phrase be deleted from the claim. At claim 11, line 2, "or" should be changed to "and" so that standard Markush terminology is used. At claim 13, line 2, it is suggested that "known" be deleted, in order to avoid the issue of what constitutes a "known" Merrifield method. For example, it is not clear if Merrifield methods which differ from typical or standard Merrifield practices in terms of, e.g., concentration, solvent, or support composition, still constitute "known" Merrifield methods. Claims 17 and 18 are indefinite because it is not clear what constitutes a "Use". It is not clear if Applicants are claiming, e.g., a method of use or a product with an intended use limitation. To the extent that the former is intended, the claims are indefinite because they are drawn to a method of use, but no positive process step is recited in the claims.

7. Claims 4-6 and 12 are objected to because of the following informalities: SEQ ID NOS must be inserted after every sequence subject to the sequence disclosure rules. See 37 CFR

1.821(d). This applies to sequences in instant claims 4, 5, and 6. Claims 4 and 5 do not end in periods. At claim 5, line 4, the first occurrence of "Met" is misspelled. At claim 5, line 7, both occurrences of "Glu" are misspelled. At claim 5, page 3 of the amendment filed August 14, 2003, line 8, the numeral "3" should be a subscript. At claim 5, page 3, line 10, the name of the antigen is misspelled. The correct spelling is "SV40-T". Compare, e.g., claim 5 as originally filed and new claim 20. At claim 12, line 4, "the" should be inserted before "active". Appropriate correction is required.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

9. Claims 1-3, 5-8, 17, 18, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 97/28822. (The examiner relies upon U.S. Patent No. 6,500,800 as a translation of the WO Patent Application '822, and all citations in the following rejections will be to the U.S. patent.) The WO Patent Application '822 teaches a conjugate comprising a transport mediator which is an internalizable ligand such as a peptide hormone, lectin, protein, sugar, or low-molecular hormone (see column 4, line 65 - column 5, line 5); a compartment-specific address peptide which can be a nuclear localisation signal such as a karyophilic sequence of the SV40 large T-antigen (see, e.g., column 4, lines 52-56); and an active substance which is a photosensitiser. See also the Abstract; column 5, lines 8-18; and Example 1, in which the transport mediator (insulin) is attached to the address protein (PI 101) which is attached to the active substance (chlorin e_6). The internalizable ligands, and especially the peptide hormones such as insulin, taught by the WO Patent Application '822 are deemed to constitute "penetratin derivatives" as claimed by Applicants in claim 3, because the peptide hormones of the WO Patent Application '822 have the same function, have the same peptide structure, and have at least one amino acid in common with penetratin. See also the above rejection under 35 U.S.C. 112, second paragraph.

10. Claims 2-4 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 97/28822 as applied against claims 1-3, 5-8, 17, 18, and 20 above, and further in

view of Blaschuk et al (U.S. Patent No. 6,303,576) or Nadler et al (U.S. Patent No. 5,877,282). The WO Patent Application '822 teaches that a wide range of transport mediators can be used, but does not teach a transport mediator which is a penetratin having the sequence specified in instant claim 4. Blaschuk et al (see, e.g., column 9, lines 25-33) and Nadler et al (see, e.g., column 8, lines 9-15) both teach that Applicants' peptide of claim 4 is a known internalization sequence which can be used to facilitate entry of a modulating agent into the cytosol of a living cell. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use as the transport mediators of the WO Patent Application '822 the penetratin of Blaschuk et al and Nadler et al, because the WO Patent Application '822 is not limited to any particular transport mediator, because Blaschuk et al and Nadler et al show that penetratin is a known transport mediator which is routinely used in the art, and because the substitution of one functionally equivalent transport mediator for another is routine and prima facie obvious in the conjugate art.

11. Claims 1-3, 5-10, 17, 18, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Gopal (U.S. Patent No. 5,670,347). Gopal teaches conjugates in which a ligand to a target receptor is conjugated to a synthetic polypeptide, optionally through a hinge region, and which is complexed with a polynucleotide. The ligand can be a neoglycoprotein, which targets the complex to hepatocytes. The ligand binds to a cell receptor, and the whole complex is taken up by the cell through receptor mediated processes. Once inside the cell, the complex enters the cell nucleus because of the presence of a nuclear localisation signal in the synthetic polypeptide. The nuclear localisation signal, which is preferably PKKKRKV, is bound to a DNA binding domain through a hinge region, and together form the synthetic polypeptide which is conjugated to the

ligand. See, e.g., column 7, lines 8-12 and 36-43, and column 8, line 50 - column 9, line 13. Gopal's ligand corresponds to Applicants' transport mediator, and is also deemed to constitute a "penetratin derivative" as claimed by Applicants in claim 3, because the ligands of Gopal have the same function as penetratin. See also the above rejection under 35 U.S.C. 112, second paragraph. Gopal's polynucleotide corresponds to Applicants' active substance and Gopal's DNA binding domain-hinge region corresponds to Applicants' spacer; or alternatively, Gopal's polynucleotide-DNA biding domain corresponds to Applicants' active substance and Gopal's hinge region corresponds to Applicants' spacer. Applicants have not defined "active substance" or "spacer" to exclude either of these interpretations.

12. Claims 1-3, 7-11, 17, 18, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Gariepy (U.S. Patent No. 5,674,977). Gariepy teaches peptide conjugates in which a cytotoxic drug such as cisplatin or acridine is conjugated through linear and branched polylysine spacers to an SV40 large T antigen nuclear localisation signal and a peptide having SEQ ID NO:3, which permits the conjugate to target breast cancer cells. The linear polylysine spacer also acts as a cytoplasm translocation domain. See, e.g., column 6, lines 5-12; column 8, lines 48-53; and column 13, line 60 - column 14, line 36. Both the peptide of SEQ ID NO:3 and the linear polylysine spacer are deemed to correspond to Applicants' transport mediator, and are deemed to constitute "penetratin derivatives" as claimed by Applicants in claim 3, because the peptide and spacer of Gariepy have the same function, have the same peptide structure, and have at least one amino acid in common with penetratin. See also the above rejection under 35 U.S.C. 112, second paragraph.

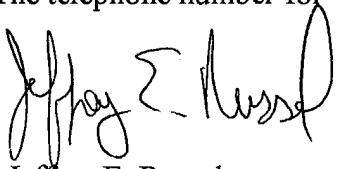
13. Claim 12 would be allowable if rewritten to overcome the claim objection set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. Claims 14-16 and 19 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 13 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. The prior art of record does not teach the particular sequence of steps recited in instant claim 12, i.e. first forming a covalent bond between AP and the active substance and then redox coupling this product with P.

14. Szoka, Jr. et al (U.S. Patent No. 5,661,025) is cited as art of interest, being essentially duplicative of the references applied above.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

PLEASE NOTE: Sometime on or around January 6, 2004, the examiner will be moving to the new USPTO headquarters. At that time, the examiner's phone number will change to (571) 272-0969. After January 6, it is recommended that Applicants attempt to contact the examiner at the new phone number if they are unable to reach him using the old number.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Technology Center 1600 for formal communications is (703) 872-9306; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1600 receptionist is (703) 308-0196.



Jeffrey E. Russel
Primary Patent Examiner
Art Unit 1654

JRussel
November 19, 2003